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BRIDGING THE DIVIDE: MECHANISTIC INSIGHTS INTO NON-ONCOLOGY DRUG REPURPOSING FOR CANCER AND NEURODEGENERATION

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ABSTARCT

For incurable illnesses like cancer and neurodegeneration, strategic alternatives are required because the traditional drug development pipeline is marked by huge expenses, longer timelines, and high failure rates. By utilizing the proven safety profiles of authorized non-oncology medications, pharmacological repurposing (DRP) presents a promising avenue. However, switching from accidental discovery to mechanism-driven validation is crucial to this strategy's success. This review offers a thorough mechanistic analysis of DRP candidates (old drugs), emphasizing medications that take advantage of the convergent pathophysiology of neurological decline and cancer by acting through non-canonical targets. We describe how common drugs, such as the cholesterol-lowering Statins and the anti-diabetic Metformin, have anti-cancer and neuroprotective effects by specifically altering common cellular markers. The Mevalonate pathway, autophagy/lysosomal dysfunction (e.g., by anti-infectives), the non-metabolic targeting of AMPK/mTOR signaling, and the complex interactions with the tumor and neuro-inflammatory microenvironments are some of the important mechanisms that are addressed.Using particular clinical trials for high-priority drugs like metformin and mebendazole in oncology, we examine the translational status of these candidates. We conclude by addressing the systemic issues, suggesting that the successful matching of current medications to new, complex disease signatures will depend on resolving intellectual property challenges, improving clinical trial design, and incorporating computational

strategies (such as AI-driven network pharmacology). DRP can hasten the delivery of safe, efficient treatments to patients with unmet clinical needs by giving priority to the elucidation of novel mechanisms.

INTRODUCTION

THE RATIONALE FOR DRUG REPURPOSING IN INTRACTABLE DISEASES

The development of novel therapeutics for complex diseases such as cancer and neurodegenerative disorders represents one of the most significant challenges in modern medicine. The conventional path of "de novo" drug discovery is increasingly constrained by its immense timelines, often exceeding a decade, and its staggering costs, which can surpass $2.5 billion per approved compound.[1] This challenge is compounded by the intrinsic biological complexity of the diseases themselves. In oncology, tumor heterogeneity and the evolution of drug resistance often render single-target therapies ineffective. In neurology, the impermeable blood-brain barrier and the multifactorial, slow-progressing nature of pathologies like Alzheimer's and Parkinson's disease present unique and formidable obstacles. There is a clear and pressing need for more efficient and pragmatic therapeutic strategies.

The Paradigm Shift to Mechanism-Driven Repurposing

In this context, drug repurposing—the application of known drugs to new diseases—has emerged as a highly promising alternative. While the historical successes of repurposing were often serendipitous, the future of the field lies in a deliberate, mechanism-driven approach. This strategy offers distinct advantages, including a well-understood human safety profile that significantly de-risks early clinical development and the potential to reduce development timelines and costs by an estimated 30-40%.[2]

The core thesis of this new paradigm is the need to move beyond chance discoveries toward a rational framework. This involves systematically elucidating the novel, non-canonical targets of existing drugs. Many pharmaceuticals exhibit polypharmacology, meaning they can interact with multiple biological pathways beyond their primary intended target. By leveraging advanced technologies in computational biology and functional genomics, we can uncover these hidden mechanisms, allowing for the intelligent redeployment of drugs against previously unconsidered therapeutic indications.

A Convergent Biological Rationale

The scientific foundation for repurposing drugs between non-oncology, oncology, and neurology fields is strengthened by a growing understanding of shared molecular pathology. Despite their divergent clinical manifestations, cancer and neurodegenerative diseases display a surprising convergence in their dysregulation of fundamental cellular processes.

Key shared hallmarks include

- **Sustained Inflammation**: Chronic activation of inflammatory pathways is a well-known driver of tumor progression and is equally implicated in the neuronal damage of neurodegenerative conditions.
- **Metabolic Dysregulation**: Alterations in cellular energy metabolism, such as the Warburg effect in cancer, find parallels in the mitochondrial dysfunction observed in many neurological disorders.
- **Dysfunctional Cell Death Pathways**: The evasion of apoptosis that characterizes cancer cells mirrors the inappropriate activation of cell death pathways that leads to neuronal loss.

This molecular convergence provides a powerful rationale.[3] A drug originally developed to modulate inflammation in arthritis may, through a precisely understood mechanism, also disrupt the pro-tumor inflammatory microenvironment or protect neurons from inflammatory insult. It is at this intersection of shared biology that mechanism-driven repurposing finds its most compelling logic.

Unveiling Novel Mechanisms: Targeting Convergent Pathophysiology

Strong clinical data supports the reuse of existing drugs for new diseases. This success is explained by the discovery that many drugs have multiple effects on core biological pathways. These pathways are often disrupted in very different illnesses. This section will examine these new mechanisms, focusing on how metabolic, inflammatory, and drug-delivery pathways are common problems in both cancer and neurodegenerative diseases. This provides a scientific basis for why drug repurposing can be effective.

Metabolic Reprogramming and Mitochondrial Function

Cellular metabolism, once considered a mere housekeeping function, is now recognized as a cornerstone of disease pathophysiology. Both cancer cells and degenerating neurons undergo significant metabolic reprogramming, creating a unique vulnerability that can be targeted by existing metabolic modulators.

Metformin and mTOR/AMPK Signaling

Metformin, a first-line therapy for type 2 diabetes, is the archetype of a drug whose repurposing potential extends far beyond glycemic control. Its primary mechanism involves the activation of AMP-activated protein kinase (AMPK), a central cellular energy sensor. This activation occurs indirectly through inhibition of mitochondrial complex I, leading to an increased AMP/ATP ratio.[4]

Cancer: Targeting the Warburg Effect and mTORC1. Many cancers exhibit the "Warburg effect," a preference for aerobic glycolysis even in the presence of oxygen. Metformin counteracts this by AMPK-mediated suppression of mTORC1 (mechanistic target of rapamycin complex 1), a master regulator of cell growth and proliferation. Activated AMPK phosphorylates and activates TSC2 (tuberous sclerosis complex 2), a potent inhibitor of mTORC1.[5] This cascade leads to the inhibition of protein synthesis and cell cycle progression. Furthermore, the direct energy crisis induced by complex I inhibition is particularly detrimental to cancer cells, which often operate on a metabolic brink. Epidemiological studies have consistently suggested a reduced cancer incidence and mortality in diabetic patients taking metformin, fueling numerous clinical trials in oncology.[6]

Neurodegeneration: Modulating Autophagy and Mitochondrial Biogenesis. In neurodegenerative contexts like Alzheimer's disease (AD), neuronal bioenergetics are critically impaired. Here, metformin's AMPK activation presents a double-edged sword, yet its potential is significant. On one hand, AMPK activation can enhance autophagic flux, the cellular clearance mechanism for dysfunctional organelles and protein aggregates like amyloid-β and hyperphosphorylated tau. This "clean-up" function is neuroprotective .[7]Concurrently, AMPK activation promotes mitochondrial biogenesis via the PGC-1α (peroxisome-proliferator-activated receptor gamma coactivator 1-alpha) pathway, potentially restoring energy production in stressed neurons.[8] However, the nuanced, context-dependent effects of sustained AMPK activation in the brain, including potential impacts on tau phosphorylation, require careful investigation in clinical settings.

Statins and the Mevalonate Pathway

Statins (HMG-CoA reductase inhibitors) are cornerstone therapies for hypercholesterolemia. Their repurposing potential, however, stems from their inhibition of the mevalonate pathway downstream of cholesterol synthesis, specifically the production of isoprenoid intermediates.

Mechanism: Disrupting Protein Prenylation. By inhibiting HMG-CoA reductase, statins deplete not only cholesterol but also downstream isoprenoids, farnesyl pyrophosphate (FPP) and geranylgeranyl pyrophosphate (GGPP). These lipids are essential for the post-translational prenylation of small GTPases, including Ras, Rho, and Rac. Prenylation facilitates their attachment to cell membranes, a step mandatory for their activation and signal transduction.[9]

Cancer: oncogenic Ras and Rho signaling drives uncontrolled proliferation, invasion, and metastasis. By disrupting the membrane localization and function of these GTPases, statins can induce apoptosis and sensitize tumor cells to conventional therapies. This mechanism is independent of their cholesterol-lowering effects and has been demonstrated in various preclinical models.[10]

Neurodegeneration and Neuroinflammation: the same small GTPases (e.g., RhoA) are critical for orchestrating pro-inflammatory signaling in glial cells (microglia and astrocytes). GGPP depletion by statins inhibits this signaling, leading to a potent anti-inflammatory phenotype in the brain. This suppression of neuroinflammation is a key mechanism proposed for the observed reduced risk of AD and Parkinson's disease (PD) in long-term statin users.[11]

Inflammation, Immunity, and the Microenvironment

Chronic inflammation is a universal driver of pathology, creating a shared therapeutic landscape for drugs that can modulate the immune microenvironment in tumors and the brain.

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) (e.g., Aspirin)

The chemopreventive effects of aspirin and other NSAIDs are historically attributed to the inhibition of cyclooxygenase (COX)-2 and the subsequent reduction of pro-inflammatory prostaglandins. However, novel, COX-independent mechanisms are increasingly recognized.

Beyond COX Inhibition: NF-κB Suppression and TIMO. A primary alternative mechanism is the direct inhibition of the NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) signaling pathway. NF-κB is a master transcription factor for pro-inflammatory cytokines, chemokines, and anti-apoptotic factors. Aspirin metabolites, such as salicylate, have been shown to inhibit IκB kinase β (IKKβ), preventing the degradation of IκB and the subsequent nuclear translocation of NF-κB.[12] In the tumor immune microenvironment (TIME), this suppression dampens the production of cytokines that support tumor survival

and immune evasion. It can also reduce the infiltration of pro-tumorigenic M2 macrophages and myeloid-derived suppressor cells (MDSCs), thereby indirectly enhancing anti-tumor immunity.

Anti-Infectives (e.g., Chloroquine): Autophagy and Lysosomal Dysfunction

Chloroquine (CQ) and its derivative hydroxychloroquine (HCQ), antimalarial and autoimmune drugs, have garnered significant interest as repurposing candidates due to their profound impact on autophagy.

Mechanism: Alkalinizing Lysosomes to Block Autophagic Flux. CQ/HCQ are weak bases that diffuse into and accumulate within acidic cellular compartments, particularly lysosomes. This neutralizes the lysosomal pH, which is essential for the activity of hydrolytic enzymes. Consequently, the final step of autophagy—the degradation of autophagosomal cargo—is blocked, leading to an accumulation of dysfunctional autophagosomes.[13]

Cancer: tumor cells often rely on autophagy for survival under metabolic stress (e.g., hypoxia, chemotherapy). By blocking autophagic flux, CQ/HCQ sensitizes cancer cells to these stressors and can induce apoptosis, leading to their investigation in numerous clinical trials as chemo-sensitizing agents.[14]

Neurodegeneration: impaired autophagy is a feature of diseases like Parkinson's (PD), where defective clearance of protein aggregates (e.g., α-synuclein) contributes to toxicity. Paradoxically, while enhancing autophagy is generally considered therapeutic, the transient and forced accumulation of autophagosomes by CQ can, in some contexts, facilitate the clearance of soluble oligomeric species by diverting them towards alternative degradation pathways. However, the primary utility in PD models has been to study the consequences of autophagic blockade, and clinical application requires careful dosing to avoid exacerbating pathology.[14,15]

Case Studies: Non-Oncology Drug Classes in Clinical Translation

Building upon the mechanistic foundations of convergent pathophysiology, we now transition to the practical application of this paradigm. This section examines specific, non-oncology drug classes that have demonstrated promising anti-cancer activity and are actively being evaluated in clinical trials. The focus here is not on preclinical rationale alone, but on the

translation of these insights into human studies, highlighting both the promise and the challenges of this approach.

Anti-Infectives and Anti-Parasitics

This class represents a rich source for repurposing due to the shared biological vulnerabilities between pathogens, parasites, and cancer cells. Their known safety profiles accelerate their entry into oncology trials.

• **Mebendazole and Microtubule Targeting:** Mebendazole, a broad-spectrum anthelmintic, exerts its anti-parasitic effect by inhibiting microtubule polymerization. This same mechanism is potently cytotoxic to rapidly dividing cancer cells. Preclinical studies have shown that mebendazole disrupts the microtubule network in glioblastoma (GBM) cells, leading to cell cycle arrest and apoptosis.[16] Importantly, it demonstrated significant survival benefits in orthotopic mouse models of GBM, including in temozolomide-resistant settings.[17] This compelling data has propelled mebendazole into clinical trials. A Phase I study (NCT01729260) in patients with recurrent high-grade gliomas established a safety profile and suggested a potential survival benefit, with results reported in **2020**.[18] Subsequent Phase II trials have further explored its efficacy, both as a single agent and in combination with standard chemotherapies.

• **Artemisinin Derivatives:** Artemisinin and its semi-synthetic derivatives (e.g., artesunate, dihydroartemisinin) are cornerstone anti-malarials. Their anti-cancer activity is multifaceted, originating from their endoperoxide bridge, which, in the presence of intracellular iron, generates cytotoxic free radicals.[19] A key area of interest is their activity against cancer stem cells (CSCs), and artemisinin derivatives have been shown to suppress key CSC maintenance pathways, including STAT3 and NF-κB signalling.[20] Clinically, artesunate has shown promise. A pilot study in colorectal cancer patients published in **2011** found that short-term neoadjuvant artesunate reduced Ki-67 proliferation markers in surgical specimens.[21]A prospective open-label Phase I study to determine the maximum tolerated dose in patients with advanced solid tumors was reported in **2017**.[22] While larger, controlled Phase III trials are needed, the existing clinical data positions artemisinin derivatives as compelling repurposing candidates.

Repurposing Cardiovascular and Metabolic Agents

Drugs targeting the cardiovascular system often have profound effects on the tumor microenvironment (TME) and systemic stress pathways, providing a robust rationale for their investigation in oncology.

• **Losartan (Angiotensin II Receptor Blocker):** Losartan's repurposing is a classic example of targeting the TME rather than the cancer cell directly. By blocking the angiotensin II type 1 receptor (AGTR1), losartan inhibits downstream signaling that promotes tumor fibrosis (desmoplasia), angiogenesis, and inflammation.[23] A critical effect in solid tumors is the reduction of tumor interstitial fluid pressure (IFP), which enhances chemotherapeutic drug penetration. Preclinically, losartan was shown to decrease collagen I production and hyaluronan synthesis in the tumor stroma, normalizing blood vessels and enhancing drug delivery.[24] This led to a landmark Phase II clinical trial in patients with locally advanced pancreatic cancer, where the addition of losartan to neoadjuvant FOLFIRINOX chemotherapy resulted in a significantly higher rate of subsequent successful resection. The results of this practice-changing study were published in **2019**.[25]

• **Carvedilol/Propranolol (Beta-Blockers):** The link between chronic stress, β-adrenergic signaling, and cancer progression is well-established. Beta-blockers, particularly non-selective ones like propranolol and carvedilol, antagonize this signaling. Epidemiological studies have been highly suggestive, reporting that beta-blocker use is associated with reduced cancer recurrence and improved survival.[26] Clinically, interventional trials are confirming this. A Phase II trial in patients with metastatic melanoma investigating the combination of propranolol with standard chemotherapy (paclitaxel) demonstrated favorable changes in the TME, with results reported in **2021**.[27] In breast cancer, a window-of-opportunity trial published in **2019** showed that short-term propranolol treatment reduced tumor cell proliferation (Ki-67).[28]

Novel Uses of Neurological/Psychiatric Drugs

The intricate interplay between neurotransmission, cellular signaling, and cancer has unveiled surprising anti-neoplastic properties for several neuropsychiatric agents.

• **Antidepressants/Antipsychotics**

The phenothiazine-derived antipsychotic **thioridazine** serves as a prominent example. It was found to selectively target leukemia stem cells (LSCs) while sparing normal hematopoietic stem cells.[29]Its mechanism involves antagonism of dopamine receptors and disruption of

lysosomal function and autophagy. A pilot clinical study in acute myeloid leukemia (AML) patients demonstrated that thioridazine, in combination with standard therapy, could reduce the LSC population; these findings were reported in **2020**.[30] Similarly, the antidepressant **sertraline** has been shown to inhibit the mitochondrial serine transporter SHMT2, disrupting one-carbon metabolism.[31] A Phase I trial exploring its combination with other anticancer agents in solid tumors was initiated and reported initial findings in **2021.**[32] These findings underscore that the molecular targets of psychoactive drugs can be co-opted by cancer cells.

Challenges and Technological Drivers for Rational Repurposing

Despite the compelling scientific rationale and potential for rapid clinical deployment, the systematic repurposing of non-oncology drugs faces significant headwinds. Overcoming these barriers requires a synergistic approach, blending novel technological strategies with evolved regulatory and business models.

Regulatory, Financial, and Intellectual Property Constraints

The most formidable challenges to drug repurposing are often not scientific, but economic and legal.

- **The Patent Gap and Lack of Incentive:** The primary barrier is the "patent cliff." Most promising repurposing candidates are generic, off-patent molecules. Without the prospect of market exclusivity, pharmaceutical companies have little financial incentive to invest the hundreds of millions of dollars required for large-scale Phase III clinical trials.[2] This creates a "valley of death" where promising preclinical and early clinical data for a generic drug fails to attract the investment needed for definitive validation.

- **Navigating the FDA 505(b)(2) Pathway:** The 505(b).[2] pathway is the principal regulatory route for repurposed drugs in the United States. It allows sponsors to rely, in part, on the FDA's previous findings of safety and/or effectiveness for an already-approved drug, potentially streamlining development.[33] However, strategic challenges remain. Success depends on generating new, robust clinical data specific to the new indication. Furthermore, securing method-of-use patents or obtaining periods of regulatory exclusivity (e.g., 3 years for new clinical investigations) is critical to justify the investment, but these are often shorter and less protective than the composition-of-matter patents enjoyed by novel drugs.[33,34]

Computational Strategies and AI Integration (The Future Pipeline)

To de-risk the repurposing pipeline and identify high-probability candidates, the field is increasingly turning to big data and artificial intelligence.

- **Signature Matching:** This approach involves comparing the "genetic signature" of a disease—derived from transcriptomic data of diseased tissues—to the "signature" of a drug—derived from gene expression profiles of cell lines treated with the drug (e.g., from the LINCS L1000 database). The goal is to find drugs that reverse the disease signature. For instance, a drug that downregulates genes overexpressed in a cancer and upregulates underexpressed genes is a putative therapeutic candidate. The Connectivity Map project was a pioneer in this field, and newer AI-driven platforms can perform these comparisons at an unprecedented scale and depth.[34]

- **Network Pharmacology:** Most diseases are not driven by a single gene but by dysregulated networks of protein interactions. Similarly, most drugs, especially those with repurposing potential, act on multiple targets. Network pharmacology uses computational models to map the complex interactions between a drug's multiple protein targets and the disease-associated network. AI algorithms can simulate how perturbing one node (with a drug) will ripple through the network to affect disease phenotypes, moving beyond a single-target paradigm to a systems-level understanding of therapeutic action.[35] This is particularly powerful for identifying drugs that can simultaneously modulate multiple hallmarks of cancer, such as proliferation and immune evasion.

Clinical Trial Design for Repurposed Drugs

Traditional, large-scale randomized controlled trials (RCTs) are often impractical for repurposed generic drugs. The future lies in smarter, more efficient trial designs.

- **Adaptive and Biomarker-Driven Trials:** To provide proof-of-concept efficiently, trials must be designed to validate the proposed mechanism of action. Adaptive trial designs allow for modifications based on interim data (e.g., dropping ineffective doses or patient subgroups), conserving resources.[36] Crucially, these trials should be biomarker-driven. For example, a trial for a beta-blocker in breast cancer should prioritize patients with high intratumoral catecholamine levels or elevated β-adrenergic receptor expression. Similarly, a trial for an autophagy inhibitor like chloroquine should include biomarkers of autophagic flux to confirm target engagement.[37] This precision ensures that a clinical signal is not diluted in

an unselected population and directly tests the mechanistic hypothesis, even in a small patient cohort.

CONCLUSION AND FUTURE OUTLOOK

The journey of drug repurposing from a serendipitous discovery to a rational, mechanism-driven discipline is well underway. Its potential to shorten development timelines and reduce costs, while providing new therapeutic options for patients with recalcitrant diseases, is too great to ignore.

Synthesis: Mechanism as the Bridge

This review has highlighted a key point: rigorous validation of non-canonical effects of drugs is essential to the future of repurposing. Epidemiological research' initial clinical correlations are only the beginning. The convincing link between a drug's initial use and its new application is provided by a thorough analysis of the underlying biology, such as metformin's impact on mTOR signaling, losartan's remodeling of the tumor microenvironment, or statins' disruption of protein prenylation—that provides the credible bridge between a drug's original use and its new application. Without this mechanistic foundation, repurposing efforts remain speculative and prone to failure in costly late-stage trials.

Key Research Directions

To fully realize the potential of drug repurposing, a concerted effort across multiple sectors is required.

- **Public-Private Consortia:** To overcome the IP barrier, new funding models are essential. Public-private partnerships, such as those pioneered by the National Cancer Institute's (NCI) Drug Repurposing Program, can de-risk early-stage clinical development for generics by providing funding, resources, and access to datasets.[38] Non-profit foundations focused on specific diseases are also increasingly playing a pivotal role in funding repurposing trials for which there is no commercial sponsor.

- **Prioritizing Convergent Pathophysiology:** Finally, research should strategically prioritize drug candidates that exhibit dual activity against the core pathophysiological hallmarks shared by multiple disease classes. The most compelling candidates are those that, for example, simultaneously target chronic inflammation (a driver of both cancer and neurodegeneration), metabolic reprogramming, and proteostatic stress. By focusing on these convergent nodes of disease biology, a single repurposing effort could potentially yield

breakthroughs across multiple therapeutic areas, offering the highest possible return on investment for medicine and public health.[39]

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